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APPLICANT:	Richard T. Dean, et al.		
SERIAL NO.:	08/236,402	EXAMINER:	A. Davenport
FILING DATE:	May 2, 1994	GROUP:	1811
TITLE:	**TECHNETIUM-99m LABELED IMAGING AGENTS**		

Box AF
Assistant Commissioner of Patents
Washington, D.C.

Sir:

DECLARATION PURSUANT TO 37 C.F.R. 1.132

In support of the above-identified application, John Lister-James states the following.

1. I received my B.Sc., with honors, in chemistry from Imperial College of the University of London in 1974, and I was awarded my Ph.D. in organic chemistry from the University of London in1981. From 1981 to 1986 I was a Research Fellow in the Nuclear Medicine Department of Children's Hospital, Boston, MA. During the same time period I was a Visiting Scientist at the Massachusetts Institute of Technology, Cambridge, MA. From 1983 to 1986, I was also an Associate in Radiology in the Nuclear Medicine Department of Harvard Medical School. During this period, my research included designing, synthesizing and modifying ^{99m}Tc radiopharmaceuticals; investigation of structure/activity relationships probing biochemical processes; and development of new methods in organic synthesis. From 1987 to 1990, I was employed at Centocor, Inc., Malvern, PA, in the Radiopharmaceutical Research & Development

Department, in a variety of senior positions. At Centocor, Inc., I supervised the product development support for, wrote sections of, and coordinated the completion of the technical sections of US and European Product License Applications for a radioimmunodiagnostic product. While at Centocor, I also supervised technical projects supporting Product License Application submissions, and I supervised a group of senior and associate scientists in the development of novel protein modification and radiolabeling methods leading to proprietary technology. I have been employed at Diatide, Inc., the assignee of the present application, since 1990, and I am currently Senior Director, Research and Development. I am a coauthor of numerous scientific publications, including the following:

1. Holman BL, Jones AG, Lister-James J, Davison A, Abrams MJ, Kirshenbaum, JM, Tumeh SS, English, RJ., A New ^{99m}Tc-Labeled Myocardial Imaging Agent, Hexakis (t-Butylisonitrile)-Technetium (I) [^{99m}Tc TBI]: Initial Experience in the Human. J Nucl Med. 25:1,350-1,355 (1984).
2. Brenner D, Davison A, Lister-James J, Jones AG., The Synthesis and Characterization of a Series of Isomeric Oxotechnetium (+5) Bisamido Bisthiolates. Inorg Chem. 23:3793-3797 (1984).
3. Holman BL, Sporn V, Jones AG, Sia STB, Perez-Balino N, Davison A, Lister-James J, Kronauge JF, Mitta AEA, Camin LL, Campbell S, Williams SJ, Carpenter AT., Myocardial Imaging with Technetium-99m CPI - Initial Experience in the Human. J Nucl Med. 28:13-18 (1987).
4. Piwnica-Worms D, Kronauge JF, Holman BL, Lister-James J, Davison A, Jones AG., Hexakis (carbomethoxyisopropyl-isonitrile)technetium(I), a New Myocardial Perfusion Imaging Agent: Binding Characteristics in Cultured Chick Heart Cells. J Nucl Med. 29:55-61 (1988).
5. Bryson N, Dewan JC, Lister-James J, Jones AG, Davison A., Neutral Technetium(V) Complexes of Amide Thiol Thioether Chelating Ligands. Inorg Chem. 27:2154-2161 (1988).
6. Bryson NJ, Brenner B, Lister-James J, Jones AG, Dewan JC, Davison A., Synthesis and Molecular Structure of a "Lantern" Dimer AsPh4)2[Tc202(SCH2CONHCH2CH2NHCOCH2S)4]. Inorg Chem. 28:3825-3828 (1989).
7. Bryson N, Lister-James J, Jones AG, Davis WM, Davison A., Protecting Groups in the Preparation of Thiolate Complexes of Technetium. Inorg Chem. 29:2948-2951 (1990).
8. Weber RW, Boutin RH, Nedelman MA, Lister-James J, Dean RT., Enhanced kidney clearance with an ester-linked ^{99m}Tc-radiolabeled antibody Fab'-chelator conjugate. Bioconjugate Chem. 1:431-437 (1990).
9. Moyer BR, Vallabhajosula S, Lister-James J, Bush LR, Cyr JE, Snow DA, Bastidas D, Lipszyc H, Dean RT., Technetium-99m-White Blood Cell-Specific Imaging Agent Developed from Platelet Factor 4 to Detect Infection, J. Nucl Med 37:673-679 (1996).
10. Vallabhajosula S, Moyer BR, Lister-James J, McBride BJ, Lipszyc H, Lee H, Bastidas D, Dean RT, Preclinical Evaluation of Technetium-99m-Labeled Somatostatin Receptor-Binding Peptides. J. Nucl Med 37:1016-1022 (1996).

11. Pearson DA, Lister-James J, McBride WJ, Wilson DM, Martel LJ, Civitello ER, Taylor JE, Moyer BR, Dean RT., Somatostatin Receptor-Binding Peptides Labeled with Technetium-99m: Chemistry and Initial Biological Studies. J. Med. Chem. 39:1361-1371 (1996).
12. Pearson DA, Lister-James J, McBride WJ, Wilson DM, Martel LJ, Civitello ER, Taylor JE, Moyer BR, Dean RT., Thrombus Imaging Using Technetium-99m-Labeled High-Potency GPIIb/IIIa Receptor Antagonists. Chemistry and Initial Biological Studies. J. Med. Chem. 39:1372-1382 (1996).
13. Lister-James J, Knight LC, Maurer AH, Bush LR, Moyer BR, Dean RT., Thrombus Imaging with a Technetium 99m-Labeled, Activated Platelet Receptor-Binding Peptide. J. Nucl Med 37:775-781 (1996).

I am a coinventor of numerous issued U.S. patents, including the following:

U.S.Pat. No. 4,673,562, issued June 16, 1987, entitled Bisamide bisthiol compounds useful for making technetium complexes.
U.S.Pat. No. 4,746,505, issued May 24, 1988, entitled echnetium diagnostic fatty acids derived from bisamidebisthiol ligands.
U.S.Pat. No. 5,162,505, issued 1992, entitled Proteins m
odified with positively changed carriers and compositions prepared theretrom.
U.S.Pat. No. 5,185,433, issued February 9,1993, entitled Cross-linking protein compositons having two or more identical binding sites.
U.S.Pat. No. 5,225,180, issued July 6, 1993, entitled Technetium-99m Labeled Somatostatin-Derived Peptides for Imaging.
U.S.Pat. No. 5,508,020, issued April 16, 1996, entitled Technetium-99m Labeled Peptides for Imaging.
U.S.Pat.No. 5,645,815, issued July 8, 1997, entitled Radiolabeled Compounds for Thrombus Imaging.

I am a coinventor of the present application.

2. I have read and understood the rejection under 35 U.S.C. sec. 112, first paragraph, of claims 1-6, 9, 10, and 19-21 now pending in the above-identified application.

3. Diatide, Inc. has conducted clinical trials of a number of reagents that fall within the scope of the present claims. For example, the somatostatin receptor binding compound *cyclo*(*N*-methyl)FYW$_D$KV.Hcy.(CH_2CO.GGCK.amide), designated as P587 in Table IV of the present application, was studied in pilot clinical trials for imaging human tumors. Technetium -99m labeled P587 did image tumors in those studies.

As another example, $\underline{CH_2CO.Y_D.Apc.GDC}GGC_{Acm}GC_{Acm}GGC$.amide, designated P246 in Table II of the present application, is the peptide component of the radiolabeled form of Acutect™, a diagnostic reagent for imaging deep vein thrombosis. This reagent has completed clinical trials, and Diatide, Inc. submitted a New Drug Application to the Food and Drug Administration on August 20, 1997. The Food and Drug Administration is reviewing the Acutect™ New Drug Application on an expedited basis, because no other imaging agent for deep vein thrombosis exists.

The somatostatin analog P829, having the structure cyclo.$\underline{(N\text{-}CH_3)F.YW_DKV.Hcy}(CH_2CO.(\beta\text{-Dap})KCK$.amide) has completed clinical trials for imaging tumors, and Diatide, Inc. is in the process of preparing a New Drug Application for submission to the Food and Drug Administration during 1998.

The glycoprotein IIb/IIIa binding compound P748, having the structure $(\underline{CH_2COY_D.Amp.GDC}KGCGamide)_2(CH_2CO)_2K(N\text{-}\varepsilon\text{-}K)GCamide$ is currently in Phase II clinical studies for imaging pulmonary emboli.

The somatostatin receptor binding compound P773, having the structure cyclo.$\underline{(N\text{-}CH_3)F.YW_DKV.Hcy}(CH_2CO.(\delta\text{-Orn})GCK$.amide), will be entering Phase I clinical trials for imaging atherosclerosis during 1998.

Each of the reagents described above contains a specific binding peptide covalently linked to a radiolabel complexing moiety having Formula I or Formula II.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Signed: _____
John Lister-James

Dated 4 Dec 97